# Extracorporeal Shock Wave Therapy: Current Evidence

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**Objectives:** The aim of this article is to provide a concise review of the basic science of extracorporeal shock wave therapy (ESWT) and to perform a systematic review of the literature for the use of ESWT in the treatment of fractures and delayed unions/nonunions.

**Data Sources:** Articles in the English or German language were identified for the systematic review by searching PubMed-MEDLINE from 1966 until 2008, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and relevant meeting abstracts from 2007 to 2008. Moreover, the bibliographies of the identified articles were reviewed.

**Study Selection:** We included clinical outcome studies of ESWT in the treatment of fractures and delayed unions/nonunions. Reports with less than 10 patients were excluded. Nonunions after corrective osteotomies or arthrodeses were excluded.

**Data Extraction:** Sample size, level of evidence, definition of delayed union, definition of nonunion, time from injury to shock wave treatment, location of fracture, union rate, and complications were extracted from the identified articles.

**Data Synthesis:** Data of 924 patients undergoing ESWT for delayed union/nonunion were extracted from 10 studies. All articles were graded as level 4 studies. The overall union rate was 76% (95% confidence interval 73%–79%). The union rate was significantly higher in hypertrophic nonunions than in atrophic nonunions.

**Conclusion:** Data from level 4 studies suggest that shock wave therapy seems to stimulate the healing process in delayed unions/nonunions. However, further investigations are required.

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## INTRODUCTION

Advances in the operative treatment of long-bone fractures continue to improve patient outcomes. About 5%–10% of the 5.6 million fractures that occur annually in the United States are complicated by delayed union or nonunion.[1] The surgical treatment of delayed unions/nonunions remains challenging and usually requires bone grafting and revision open reduction and internal fixation. With modern state-of-the-art surgical techniques, the majority of nonunions can be treated successfully.[2–5] However, the surgical treatment is usually associated with additional hospital days, comorbidity from the surgical procedure, and significant socioeconomic costs.[6] In an effort to decrease patient morbidity and health care costs, the use of noninvasive methods, such as the extracorporeal shock wave therapy (ESWT), seems to be a valuable alternative in the treatment of delayed unions and nonunions.

ESWT has been suggested for the treatment of various musculoskeletal disorders such as plantar fasciitis, lateral epicondylitis, calcifying tendinitis, and avascular necrosis of the femoral head.[7–13] Moreover, ESWT has also been suggested as a stimulator of bone healing, and it has been employed in the treatment of delayed union/nonunion.[14] The exact pathway by which ESWT may exert its effect on bone healing remains the subject of ongoing experimental investigations. The aim of this article is to provide a concise review of the basic science of ESWT on fracture healing and to systematically review the current evidence in the literature for the use of ESWT in the treatment of fractures and delayed unions/nonunions.

## BASIC SCIENCE OF ESWT

Shock waves are single high-amplitude sound waves generated by electrohydraulic, electromagnetic, or piezoelectric methods that propagate in tissue with a sudden rise from ambient pressure to its maximum pressure at the wave front, followed by lower tensile amplitude.[15] According to the International Society for Medical Shockwave Treatment (ISMST) (www.ismst.com; accessed December 22, 2008), a shock wave is defined as a sonic pulse characterized by a high peak pressure (500 bar), a short life cycle (10 ms), fast pressure rise (<10 ns), and a broad frequency spectrum (16–20 MHz). The shock waves are focused to a zone of highest energy in front of the applicator and therefore reach highest energy concentration in the focus zone within the treated tissue. The most important mechanical effects of shock waves are reflection with pressure and tension forces at borders of different impedances and the generation of cavitation bubbles in liquids. These vacuum bubbles typically collapse asymmetrically and induce local shear forces by high velocity liquid streams (so-called "jet streams").[15–17]

Several authors have investigated the biologic effects of ESWT on the molecular level.[18–30] Two major mechanisms seem to be involved in the translation of mechanical shock wave energy into its biological effects. These include membrane hyperpolarization and the formation of free radicals. Wang et al and Chen et al demonstrated shock waves to induce hyperpolarization of cell membranes, followed by Ras activation and a local increase of stimulating factors like transforming growth factor β1, vascular endothelial growth factor (VEGF) A (VEGF-A), and mitogen-activated protein kinases.[19,25–27,30] Furthermore, shock waves have been shown to produce oxygen radicals, which are supposed to play a key role in translating the mechanical energies of the shock waves into biological effects.[30] Wang et al demonstrated that oxygen radical production induced a cascade of kinases and growth factors, such as VEGF, transforming growth factor β1, BMP-1, BMP-2, and BMP-7, which was followed by an increased growth and differentiation of mesenchymal cells toward osteoprogenitor cells.[25–30]

The effect of ESWT on fracture healing in vivo has been investigated in numerous studies using different animal models. Although some investigators did not observe any positive effects of ESWT on bone healing in their in vivo models,[31–33] numerous authors reported a stimulating effect of ESWT on bone formation in vivo using different animal models.[22,24,34–37] In vivo studies in rabbits demonstrated that exposure of normal bone to ESWT may result in increased new bone formation.[34] Further investigations using fracture models in rats, rabbits, and dogs showed increased callus formation, decreased healing time, and increased mechanical strength of broken bones with exposure to ESWT.[22,24,35] In the most recent study using a fracture model in rabbits, Wang et al[37] observed a significantly better bone strength, more cortical bone formation, a higher number of neovessels, and increased angiogenic and osteogenic growth markers including VEGF, endothelial nitric oxide synthase, proliferating cell nuclear antigen, and BMP-2 in animals undergoing ESWT treatment as compared with the control group. Johannes et al[36] investigated the effect of ESWT using a nonunion model in a dog. These authors reported that ESWT exposure resulted in increased healing rates in established nonunions as compared with a control group.[36]

The dose-dependent effect of the ESWT has been the subject of several investigations. Dose-dependent stimulation of bone cells in vitro was observed by Kusnierczak et al[38] after shock wave application, with a minimum threshold energy necessary to effect bone cell growth. Bone cell stimulation seemed to depend on the total amount of energy applied, rather than on single physical parameters like energy flux density or number of administered impulses. Furthermore, these authors reported decreased cell survival with excessive energy flux densities. These findings from in vitro studies were confirmed in subsequent in vivo studies demonstrating a dose-dependent effect of ESWT on bone mass and bone strength in acute fracture models in rabbits and in bone defect models in rats.[18,21,24] In addition, Maier et al[39,40] provided further in vivo data on the deleterious effects of very high energy flux densities, which were associated with soft tissue edema, cortical fractures, periosteal detachment, intraosseous bleeding, and even displacement of bone fragments to pulmonary vessels.

## CURRENT EVIDENCE

### Data Sources and Study Selection

A systematic review of the current literature was performed to identify clinical outcome studies of ESWT in the treatment of fractures and delayed unions/nonunions. The review included original studies with a minimum of 10 patients undergoing ESWT for treatment of fracture or fracture nonunion published in English or German. Data from book chapters and review articles were not included. Studies on pediatric patients or congenital pseudarthrosis were not considered. Studies on nonunions after corrective osteotomy or arthrodesis were excluded. In mixed series that included nonunions after fracture treatment together with nonunions after corrective osteotomy or arthrodesis, we extracted the data of fracture nonunions. If extraction of data was not possible and more than 25% of the nonunions were not related to fractures, the article was excluded from this systematic review. Redundant publications, such as meeting abstracts with subsequent full-text article publication or repeat analysis of previously published data, were excluded. Likewise, we considered articles redundant if the subjects from 2 different articles were recruited at the same institution over the same period. If there were questions regarding possible redundancies or the indication for treatment, we contacted the corresponding authors by e-mail to clarify these issues. The following databases were searched: PubMed-MEDLINE (1966 to December 2008), Cochrane Database, online archives of the 2007 and 2008 meeting abstracts of the American Academy of Orthopaedic Surgeons, online archives of the 2007 and 2008 meeting abstracts of the Orthopaedic Trauma Association (OTA), online archives of the 2007 and 2008 meeting abstracts of the ISMST, and the bibliographies of identified articles.

### Identified Studies

A total of 11 relevant studies that met our inclusion criteria were identified (9 full-text publications and 2 meeting abstracts) and were included into our systematic review of the literature.[14,41–50] The database searches yielded the following articles:

1. PubMed-MEDLINE: the search terms "(shock wave* OR shockwave* OR lithotrips*) AND (fracture* OR nonunion* OR pseudarthros*)" resulted in 169 hits. A total of 10 articles were found to be relevant and matched the inclusion criteria.[14,41,42,45,46,48–52] Two of these 10 studies[51,52] were excluded because the published data were redundant and were subsequently republished in a later article.[45]
2. Cochrane Database: the search terms "(shock wave* OR shockwave* OR lithotrips*) AND (fracture* OR nonunion* OR pseudarthros*)" were used to search the Cochrane Database of Systematic Reviews (6 hits, none relevant), the Cochrane Database of Abstracts of Reviews

of Effects (1 hit, not relevant), and the Cochrane Central Register of Controlled Trials (4 hits, 1 relevant but redundant as the same article had been identified in the PubMed search[49]).
3. Online archives of the meeting abstracts of the American Academy of Orthopaedic Surgeons: the 2007 and 2008 meeting abstracts were manually reviewed. One relevant study was identified[53] but was redundant with subsequent full-text publication.[49]
4. Online archives of the meeting abstracts of the OTA: the 2007 and 2008 meeting abstracts were manually reviewed. No relevant studies were identified.
5. Online archives of the meeting abstracts of the ISMST: the 2007 and 2008 meeting abstracts were manually reviewed. Three relevant studies were identified,[44,47,54] and 1 was excluded[54] because the data redundant and re-presented at the same meeting.
6. Review of bibliographies of the identified articles yielded one relevant study that matched the inclusion criteria.[43]

Of 11 articles enrolled into this systematic review, 10 articles[14,41–48,50] reported on shock wave therapy in fracture nonunion/delayed union, whereas 1 article[49] dealt with shock wave therapy in the treatment of acute fractures.

## Data Extraction

The following parameters were abstracted from the identified articles: sample size, level of evidence, definition of delayed union, definition of nonunion, time from injury to shock wave treatment, location of fracture, union rate, and complications. The union rate was the primary outcome measure of this systematic review. The level of evidence was graded into the evidence-based medicine levels 1–5, according to *Journal of Bone and Joint Surgery* levels of evidence (http://www2.ejbjs.org/misc/instrux.dtl#levels; accessed December 22, 2008).

## Data Analysis

The data on delayed unions/nonunions were analyzed descriptively. Comparisons between shock wave therapy versus control group or versus other treatments were not possible because there were no higher level studies. The overall union rates were calculated. The union rates between atrophic nonunions and hypertrophic nonunions were compared using the Fisher exact test.

## Results

The available evidence of the 11 identified studies was graded as follows:
1. Ten case series (level 4) reporting on the outcomes of shock wave therapy in the treatment of delayed unions/nonunions.[14,41–48,50]
2. One prospective randomized clinical trial (level 2) comparing operative treatment of acute femur and tibia fractures versus operative treatment plus shock wave therapy.[49]

From the 10 articless reporting on shock wave therapy in the treatment of delayed union/nonunion, a total of 924 patients were extracted [14,41–48,50] (Table 1). These included 148 delayed unions and 694 nonunions, and in 82 patients, the authors did not distinguish between the 2. The most common definition of delayed union was no healing at 3–6 months (n = 143). In 5 cases, the definition of delayed union was not provided by the authors. The definition of nonunion was as follows: no healing at a minimum of 6 months after injury (n = 509), no healing at a minimum of 9 months (n = 17), not extractable (n = 168). The anatomic fracture location was mixed in all series. The mean time from injury to shock wave treatment was 13 months (range 3–300 months). The exact fracture location was extractable for a total of 364 fractures and was distributed as follows: humerus, 36; radius, 32; ulna, 23; metacarpal, 8; scaphoid, 45; other upper

**TABLE 1.** Overall Outcomes in Delayed Unions/Nonunions

| Study | n | Minimum Time From Injury to ESWT | No. Treatment Sessions | Union Rate | Union Rate Atrophic Versus Hypertrophic |
|---|---|---|---|---|---|
| Valchanou et al[14] | 82 | — (mean: 20 mo) | 1 | 70/82 | — |
| Beutler et al[41] | 27 | 6 mo | 2 | 11/27 | Atrophic: 3/12<br>Hypertrophic: 8/15 |
| Biedermann et al[42] | 23 | 6 mo | 1–2 | 13/23 | — |
| Diesch et al[43] | 142 | — | 1–3 | 102/142 | Hypertrophic: 102/142 (only hypertrophic NU included) |
| Guiloff et al[44] | 31 | — (26 NU/5 DU) | 1–3 | 21/31 | — |
| Rompe et al[45] | 17 | 9 mo | 1 | 10/17 | — |
| Schaden et al[46] | 115 | 3 mo (n = 35)<br>6 mo (n = 80) | 1 | 87/115 | — |
| Valentin et al[47] | 349 | 3 mo (n = 108)<br>6 mo (n = 241) | 1–2 | 282/349 | — |
| Wang et al[48] | 72 | 6 mo | 1 | 44/55 (17 lost to FUP) | Atrophic: 6/8<br>Hypertrophic: 25/31<br>Fracture gap: 13/16 |
| Xu et al[50] | 66 | 6 mo | 1 | 50/66 | Atrophic: 0/11<br>Hypertrophic: 50/55 |

DU, delayed union; ESWT, Exracorporal shock wave therapy; FUP, follow-up; n, number of fractures; NU, nonunion.

extremity fractures, 11; pelvis, 3; femur, 91; patella, 1; tibia, 94; fibula, 1; midfoot, 3; talus, 2; metatarsals, 2; and other lower extremities 12. The number of impulses was highly variable. All articles identified in this systematic review documented between 1 and 3 treatment sessions.

The overall union rate in patients with delayed union/nonunion was 76% (95% confidence interval 73%–79%) and ranged from 41% to 85%. For 274 injuries, the authors distinguished between atrophic nonunions (n = 31) and hypertrophic nonunions (n = 243). The union rate in atrophic nonunions was 29% (9 of 31) as compared with 76% (185 of 243) in hypertrophic nonunions (relative risk = 2.6; 95% confidence interval 1.6–4.7; $P < 0.0001$). The only recorded complications included local swelling, petechiae, and hematoma. Only 1 article provided the incidence of these complications (petechiae 81% and hematoma 38%).[48]

Only 1 article reported on the clinical outcomes of shock wave therapy in the treatment of acute long-bone fractures.[49] These authors reported a level 2 study including 56 patients with 59 fractures of the femur and/or tibia. Patients were allocated to operative fixation plus intraoperative shock wave therapy versus operative fixation without shock wave therapy. The minimum follow-up was 12 months. The authors observed a higher nonunion rate in the control group than in the shock wave therapy group (11% vs. 20%) and suggested shock wave therapy as effective in decreasing nonunion rates in acute long-bone fractures.

### Grades of Recommendation

The overall quality of the literature on shock wave therapy in fracture healing was graded according to the *Journal of Bone and Joint Surgery* grades of recommendation.[55] In this grading system, the grades of recommendation are defined as follows: grade A, good evidence (level 1 studies with consistent findings); grade B, fair evidence (level 2 or 3 studies with consistent findings); and grade C, conflicting or poor-quality evidence (level 4 or 5 studies) not allowing a recommendation, grade 1, insufficient evidence to make a recommendation.

Based on this grading system, a grade C recommendation can be given for shock wave therapy in the treatment of delayed union/nonunion because the available evidence is limited to level 4 studies. No recommendation can be made with regards to the treatment of acute fractures because only one peer-reviewed article was identified in our systematic review.

## DISCUSSION AND CONCLUSIONS

The treatment of fracture nonunions remains a challenging problem for trauma surgeons. Treatment approaches that minimize patient morbidity and treatment costs seem desirable. Experimental data suggest that shock wave therapy may stimulate bone formation in vitro and in vivo.[18–30,34–38] However, the clinical use of shock wave therapy in the treatment of fractures and delayed unions/nonunions is not widely established. Our data from level 4 studies suggest that approximately three-fourth of delayed unions/nonunions can be treated successfully using this approach. Moreover, the currently available evidence suggests that hypertrophic nonunions show a better response to this approach than atrophic nonunions.

Our study has both strengths and limitations. One limitation of our study is the lack of higher level evidence. With the data available, it is not possible to estimate how shock wave therapy compares with other treatment approaches. The extracted data of our systematic review include a relatively high number of delayed unions. The natural history of these lesions remains unclear, and it may be assumed that some of these delayed unions may have healed using other nonoperative treatment approaches. Moreover, we acknowledge that the interpretation of our data is limited by the nonstandardized definitions of delayed union and nonunion and the highly variable distribution of the anatomic fracture locations. In addition, the treatment protocols recorded in the identified studies were highly variable with regards to the number of treatment sessions and the physical parameters of the applied shock wave therapy.

The data obtained in our study support previous reports, encouraging the use of shock wave therapy. In 2002, Birnbaum et al[56] published a systematic review on shock wave therapy in the treatment of nonunions and reported success rates ranging from 75% to 91%. However, these authors did not report their search strategies, and the majority of their data were obtained from non–peer reviewed literature, such as book chapters. For these reasons, the validity of their data remains unclear. We believe that the thorough search of different databases and the well-defined inclusion criteria allow us to assume that the data extracted in our systematic review is a robust representation of the currently available evidence of shock wave therapy in the treatment of delayed union/nonunion.

We conclude that the currently available evidence for shock wave therapy in the treatment of delayed union/nonunion is based on level 4 data. The available studies suggest that approximately three-fourth of delayed unions/nonunions can be treated successfully using this approach. Future studies need to investigate how shock wave therapy compares with other treatment approaches and if different anatomic fracture locations may demonstrate different success rates. Moreover, the optimal treatment dose needs to be identified in further investigations. No conclusions can be made with regards to shock wave therapy in the treatment of acute fractures because only 1 identified study investigated this topic.

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